A Business Model for a New Generation Of Diagnostics Companies

Venture capital has tended to shy away from diagnostics companies, whose products are not predicated on the blockbuster model of pharmaceuticals. But several new diagnostics companies are developing products that hold immense potential to improve healthcare delivery. Here's why venture investors should take another look at the diagnostics area.

Gary Kurtzman, MD
BioAdvance

Medicine is changing. As a physician and long-time biotechnology entrepreneur, I see firsthand the newly emerging but growing impact of the "omics" (genomics, proteomics, cytomics, metabolomics) revolution. Developments in these areas are changing the way we understand and treat disease, as well as how we discover and develop drugs. This dynamic transformation is accelerating, as new biomedical technologies and tools become easier to use and less expensive. The effects of this revolution are already evident in day-to-day medical care in the field of *in vitro* diagnostics (IVD).

Author correspondence:

Gary J. Kurtzman, MD
BioAdvance
3701 Market Street
Philadelphia, PA 19104
Phone: (215) 966-6217
E-mail:
gkurtzman@bioadvance.com

Advances in biomedicine are combining to link genetics, gene expression, and disease diagnosis and treatment in a way that was never before possible. We now are able to begin to determine the best treatment approach for some cancers, based on the genetics of the tumor or the genetic makeup of the patient. The shift from a one-size-fits-all approach to treatment regimens that are tailored to individual patients' needs — the promise of pharmacogenomics or personalized medicine — has begun and is expected to gain greater momentum in coming years.

As a result of these advances, new diagnostic technologies are providing us with wholly new capabilities. We are entering an era where we will have the ability to predict disease susceptibility, detect disease with greater accuracy and at an earlier stage, and predetermine an individual's response to drugs. Diagnostics — including the fields of molecular diagnostics, molecular imaging, and biomarkers — are at the center of this change.

At BioAdvance, The Biotechnology Greenhouse of Southeastern Pennsylvania, we are using our $33 million in tobacco-settlement funds to invest in new life sciences enterprises. In just a little more than two years, we have helped to promote 29 startup companies and academic projects. The following diagnostics ventures are among those in the BioAdvance portfolio:

- **Avid Radiopharmaceuticals** is developing novel approaches to diagnosing Alzheimer's disease, other neurodegenerative diseases, and cancer
- **Cira Discovery Sciences** is applying pattern discovery to develop the next generation of diagnostics based on proteomic information
- **Eagle Vision** currently has a noninvasive diagnostic agent in clinical testing that will enable cardiologists to assess blood flow to the heart

- **RetinaPharma** markets TonoPach, a device recently approved by the U.S. Food and Drug Administration to improve ease and accuracy of diagnosing glaucoma
- **SonoMedix** is developing convenient, home-based systems to monitor blood coagulation

Our experience at BioAdvance has provided valuable lessons about what does and does not work for companies that are vying for early-stage funding. Despite our enthusiasm for diagnostics, diagnostic startups generally have had trouble obtaining venture financing. I believe that several fundamental factors underlie this situation. The most important is that, often, the diagnostics business model is neither understood nor appreciated by venture capitalists — and, too often, for good reason. The good news, though, is that solutions exist, and several new diagnostics companies have the elements that are essential to securing equity financing and building a sustainable and successful business.

Gary Kurtzman MD

DIAGNOSTICS, RISING SLOWLY

A variety of factors make diagnostics a field whose time has come. Although diagnostic expenditures represent less than 5 percent of total national healthcare expenditures, correct diagnosis and treatment of disease greatly affects the other 95 or so percent of our nation's $1.7 trillion healthcare bill. With an aging population and the availability of new, expensive medical technologies driving up total costs, the need to allocate resources more cost-effectively is the biggest factor supporting wider use of predictive diagnostic tests. Diagnostics can do more than help save money; there is technology available that can make existing drug therapies safer and more efficacious.

Consumer involvement in healthcare decision making also is accelerating the pace of change. These trends are supported by a new emphasis on translational research to apply advances in knowledge and technology to medical care. The diagnostics field represents an outstanding example of how new knowledge can be applied swiftly to the delivery of health care.

Much of the focus in this field now is on molecular diagnostics, which I define as including all tests and methods to identify a disease, determine its course, evaluate response to therapy, or identify one's predisposition to a disease by analyzing one's DNA, RNA, or proteins.

Molecular diagnostics encompasses those tests that are based on a fundamental understanding of normal biological processes and how they are involved in the pathogenesis of disease.

This area represents a small proportion of all diagnostics expenditures today, but Leomics Associates, a New Jersey-based molecular diagnostics consulting firm, estimates that it will increase from the current level of $2 billion in U.S. revenues to around $8 billion by 2010.

Drivers underlying the expected rapid adoption of these new diagnostics include the growing cost of drug therapy, rapid increases in the costs of drug development (including clinical trials), and — most importantly — our increasing ability to target therapies to patients on the basis of their genetics or the genetics of their disease. This ability will enable drug developers and prescribers to conserve resources by reserving therapies for patients in whom they will be safe and effective.

Recent successes with targeted therapies, including trastuzumab (Herceptin) for breast cancer, gefitinib (Iressa) for lung cancer, and isosorbide (BilDil) for African Americans with congestive heart failure (in this case, using ethnicity as a surrogate marker for genetic differences in drug response) have highlighted the tremendous potential of pharmacogenomics.

Currently, more than 100 clinical trials of targeted new therapies are under way for cancer indications alone. The FDA supports this trend, encouraging drug developers to include pharmacogenomic studies as part of the drug discovery and development process. Because targeted therapies typically require an accompanying diagnostic test to identify candidates for the therapy, the launch of these new drugs should increase the value of companies marketing molecular diagnostics.

TEPID INTEREST

Despite the clinical and commercial promise of molecular diagnostics and the great advances in technology that make routine use of

this approach feasible, venture capital (VC) investment in diagnostics companies has remained minimal; according to *BioCentury,* only about 3 percent of all healthcare VC dollars were allocated to diagnostics companies in 2004.

Why are venture investors hesitant, despite an opportunity to invest in a field seemingly poised for major commercial growth?

Certainly, skepticism is to be expected, given the promise of large and rapidly rising revenues by a multitude of genomic enterprises launched in the boom years of 1999 to 2001 that failed to materialize for investors. After that experience, venture investors understandably come to meetings carrying a resolute "show me" attitude.

Diagnostics startups also are hampered by the fact that they generally serve smaller markets than pharmaceuticals, with little promise of the blockbuster phenomenon that fuels investor enthusiasm. Compounding the situation is fear of the lower margins that traditionally have characterized much of the diagnostics industry. Fierce competition and commoditization of routine services has driven down prices and margins in the large service sector that dominates the field.

Another major deterrent to venture investment is third-party payment. The many uncertainties about who will pay for the new generation "prognostic" assays, as well as the extent to which third-party payers will adequately cover the costs of new tests, exacerbate concerns about price-and-margin restrictions. Despite the promise of far greater efficiency and effectiveness from pharmacogenomic-guided therapies, insurers may be reluctant to pay in the absence of guarantees of near-term, tangible financial benefits. Payers may not be won over easily by studies that show benefits to patients but limited cost savings, and they may balk at paying for disease-susceptibility testing — where the payoff from lifestyle changes, prophylactic measures, and early diagnosis may be far in the future.

Regulatory issues can be just as confounding for investors. While pharma companies confront the reality of a shift from the blockbuster model of drug development to new models focused on targeted or personalized therapies, there are few role models, nor is there a clear regulatory path for the codevelopment of diagnostic and therapeutic tools.

Two reasons investment in diagnostics is attractive today: Technological advances are facilitating the discovery of better biomarkers, and earlier revenues are possible than with therapeutics.

These environmental factors are not the only hurdles to greater VC investment in diagnostics. Compounding the problem further is the fact that venture investors do not fully understand the IVD company model — a situation that is made worse by the fact that too few of the new diagnostic ventures have articulated a compelling business model.

In assessing potential diagnostics investments, venture investors bring along their preferences for candidates with strong potential return on investment (ROI), near-term revenues, a predictable regulatory environment, a generous (or at least manageable) reimbursement climate, and tangible ways to manage risk. Based on the factors described above, VCs do not see how most diagnostics ventures can score well using these criteria.

REASONS TO LIKE THE FIELD

So, as an institutional investor in diagnostics, why am I bullish? I believe that future leaders in the new diagnostics space have the potential to return handsomely on the ROI criterion. In some ways, they mimic the specialty pharmaceuticals model that has been a favorite of life sciences VCs for the past few years.

Optimally focused diagnostics ventures require much lower up-front investments than do traditional biotech enterprises to reach revenue generation, thus reducing the amount of investment required to achieve an exit for investors. Although the most likely exits will be through acquisition, I believe the possibility exists for at least a few of the significant players to integrate revenues from research and development and from service, and to build significant diagnostic franchises.

In all this, technology is a key enabler. High-throughput, multiparametric analysis of nucleic acids and proteins in normal and diseased tissue is facilitating the discovery of more informative biomarkers. The

establishment of highly annotated biobanks of tissue, DNA, and other biological samples is facilitating rapid validation of those markers. The development of platforms, particularly those based on micro- and nanotechnology, ultimately will enable the translation of these new biomarkers into useful assays in the clinical testing lab.

Another enabler is a regulatory process that can be simpler and more straightforward than that for drugs. Importantly, products can be brought to the point of revenue generation without extensive FDA oversight as "in-house developed" or "home brew" tests in a CLIA-certified reference laboratory to perform tests of "high complexity." As a result, revenue can be generated by running these tests while additional clinical data are being collected. Depending on the particular test, full FDA review then can proceed under the less rigorous 510(k) process or through a more extensive premarket approval application.

In the diagnostics space, a company with a compelling platform capable of yielding a pipeline of diagnostics can move rapidly through the research and development process to commercial launch, and do this in an iterative way. Revenues can be generated early by performing tests in the reference lab while the decision is being made whether to commercialize and market the tests oneself, develop a partnership with exiting IVD manufacturers, or out-license.

Company snapshot: XDx
AlloMap, launched in April, targets the postcardiac transplant market. AlloMap is performed in XDx's reference lab and is priced at $2,950, which is seemingly high until one realizes that it replaces an invasive biopsy costing upward of $5,000.

Another possible new business approach is a mixed product-and-service model, whereby companies can reap the financial rewards of their unique diagnostic assays while participating in the margins from the service element of the business.

In this model, discovery and development of new markers is layered on an existing menu of tests performed in a reference lab. The value here is the potential to move diagnostics and platforms rapidly from discovery phase through validation, using an established infrastructure that includes operational, regulatory and reimbursement expertise.

WHAT MAKES SUCCESS?

We already have examples of new IVD companies that have attracted significant investment from VC and other sources of capital. The following represent three of these examples:

ViroLogic (see box below) is leveraging its diversified product base in HIV, immunologic, and cancer testing to build a sustainable, high-growth business that seems well positioned to prosper as pharmacogenomics and molecular testing become more widely used. A pioneer in developing genomic assays to help physicians monitor and tailor therapy for HIV patients, ViroLogic has an established reference lab to assay patient samples and a service business to support biopharmaceutical companies developing treatments for HIV and cancer.

A public company, ViroLogic generated revenues of more than $36 million in 2004, and has a market capitalization of more than $300 million.

XDx, another top-tier, venture-backed molecular diagnostics company, is applying microarray, real-time polymerase chain reaction (or PCR, a technique for amplifying a selected region of a DNA molecule) and other bioinformatics technologies to develop new ways to monitor the immune system.

The success of the XDx AlloMap molecular expression profile test (see box, above) recently led venture backers to reward XDx with $20 million Series D financing.

Yet another pioneer illustrating the potential of this new business model is **Genomic Health,** which has top-tier VC financing (including the firm that first funded Genentech), and it has begun commercializing its first product as a home brew.

Data generated in its clinical studies, recently reported in the *New*

Company snapshot: ViroLogic
In its mission statement, ViroLogic defines itself as "committed to advancing individualized medicine by discovering, developing, and marketing innovative products to guide and improve treatment of serious viral, immunologic, and oncologic diseases."

Company snapshot: Genomic Health

- Innovation inherent in its research-based approach
- Clinically validated pharmacogenomic approach
- Well-capitalized financial structure
- Investment in leading-edge science
- Proprietary high-margin nature of its first product
- Reference lab approach
- Sophisticated early-marketing efforts

England Journal of Medicine, support its Oncotype DX test measuring the expression of a number of selected genes in breast cancer as being more predictive of patient outcome than standard pathology testing. The new test is intended to help physicians and patients make rational decisions about the management of newly diagnosed breast cancer.

The features listed in the box at the top of this page make Genomic Health a good model for future VC-backed ventures. Consistent with its first-mover status, Genomic Health recently announced the filing of an S-1 registration with the U.S. Securities and Exchange Commission for its initial public offering.

LESSONS LEARNED

As BioAdvance considers investing in these new-era molecular diagnostic firms, what lessons have we learned from our examination of the field?

1. The combination of proprietary technology and demonstrable clinical and economic benefits is key. Successful companies focus on assays that address an underlying biology or disease state, and apply high-throughput techniques and bioinformatics technologies to identifying valuable biomarkers.

2. The pipeline is essential — IVD companies need a platform for developing and launching the multiple pipeline products needed for commercial success.

3. Access to patient data also is a necessity — validation is required from large patient cohorts, both from well-annotated banked specimens and well-designed and executed clinical studies.

4. Establishing early proof of the company's ability to generate revenues is important. The establishment of an in-house reference laboratory provides revenue, as well as the means for data generation and early acceptance by healthcare providers.

5. Building regulatory experience, from operating a clinical reference lab and through design and execution of validation studies and clinical trials, is critical.

6. A strategy that ensures adequate third-party payment will be challenging, but it is essential. Securing this will necessitate a proactive, collaborative, and sustained efforts.

POLICY CHANGE NEEDED

I believe that the positive changes in medicine from the "omics" revolution largely will be driven in the coming years by new, more predictive diagnostic tests. Commercialization of these tests will provide significant rewards for patients who will receive improved medical care, as well as for the investors who will obtain attractive investment returns.

Yet there is a potential monkey wrench in this otherwise promising picture — the issue of third-party payment. Without fair and consistent policies governing payment for this new generation of diagnostic tests, the commercial and clinical potential of these powerful new tools could remain largely unrealized. This necessitates a major policy change that will not take place unless the value of these new diagnostics in the delivery of medical care is better quantified and documented.

Such a change also will necessitate proactive efforts by many participants. We therefore look to life sciences researchers, medical providers, diagnostic companies, forward-looking biotech and drug companies, trade organizations, and advocacy groups to contribute to the process needed to bring about this shift.

At BioAdvance, we believe that the new era of molecular diagnostics is an idea whose time has come. We intend to continue to work with the rich life sciences resources available in our region to support the development and venture funding of new enterprises that will help drive the coming revolution in targeted and personalized healthcare, with all the benefits to individuals, the healthcare system, and society that these innovations make possible. BH

Gary Kurtzman MD, is managing director and chief operating officer of BioAdvance, the Biotechnology Greenhouse of Southeastern Pennsylvania.